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EXAMINER	
JAGOE, DONNA A	
ART UNIT	PAPER NUMBER
1619	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,000	ARBER ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,9-15,20,21,23-25 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,9-15,20,21,23-25 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments/Arguments

Claims 1, 3-5, 9-15, 20, 21, 23-25 and 32 are pending in this application.

Applicant's amendments and arguments filed June 17, 2010 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below in original or modified form is herein withdrawn.

Applicant asserts that the claims rejected under 35 USC §112, first paragraph should be withdrawn in view of the cancellation of claims 7, 16, 19, 26-28, 30 and 24. This argument is unpersuasive. The following considerations pertain:

In terms of the law, MPEP 2107.03 states "evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. Cross v. Iizuka, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); In re Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881 (CCPA 1980)." If correlation is lacking, it cannot be relied upon, Ex parte Powers, 220 USPQ 924; Rey-Bellet and Spiegelberg v. Engelhardt v. Schindler, 181 USPQ 453; Knapp v. Anderson, 177 USPQ 688. Indeed, the correlation must have been established "at the time the tests were performed", Hoffman v. Klaus, 9 USPQ2d 1657.

In this case, applicants have not asserted, let alone established, that their particular tests are orrelated with the claimed utility. Applicants are silently assuming

that this is the case. In fact, preclinical cancer models, which are principally in vitro cell studies and transplanted tumors (xenografts) have long been understood to have a particularly poor track record and, specifically, do not correlate with actual success in the treatment of cancer. The quotes which follow express this idea in a variety of ways. ("The fundamental problem in drug discovery for cancer is that the model systems are not predictive at all," says Alan Oliff, executive director for cancer research at Merck Research Laboratories. (Gura, Science 7 November 1997: Vol. 278. no. 5340, pp. 1041 – 1042); MIT Professor Robert Weinberg states: "A fundamental problem which remains to be solved in the whole cancer research effort, in terms of therapies, is that the preclinical models of human cancer, in large part, stink." (Leaf, Clifton, Health Administrator Vol. XVII, Number 1: 172-183, 2005); Says Dr. Sally Burtles, Director of Drug Development at Cancer Research UK: "We do trials in people because animal models do not predict what will happen in humans" ("EXPERT SCIENTIFIC GROUP ON PHASE ONE CLINICAL TRIALS FINAL REPORT" 30th November 2006, pages C1, C35-C38; see page C38); "Preclinical efficacy models in cancer drug discovery … are usually rodent models bearing a transplantable tumor. Yet the vast majority of these investigational drugs fail to meet their pre-specified clinical benefit or efficacy endpoints." Cancer Drug Design and Discovery Neidle, Stephen, ed. (Elsevier/Academic Press, 2008) page 427; "The poor performance of most investigational cancer drugs implies that the standard preclinical disease models are faulty or, at least, improperly used." Kamb, Nature Reviews Drug Discovery 4, 161-165 (February 2005);

A direct measure of the low predictive value of preclinical screening for anti-cancer drugs is the low rate of response for Phase 1 clinical trials. Roberts, Jr et al., JAMA 292(17): 2130-2140 (2004), Table 4, shows response rates for the 1999-2002 period ranging from 0.4% to 5.3%; the overall response rate was 3.8%. Percentages this low clearly indicate that the pre-clinical screening as a whole is absolutely not predictive --- even a rate 10 times that high would indicate that the preclinical tests are not reliably predictive. Indeed, the article notes that the response rate to these agents is actually going down over time. Moreover, Roberts, Jr reports that only 44% of the studies were actually published, and since surely studies with unfavorable outcomes are less likely to be published, the actual success rate would be below that 3.8%.)

Another approach is to look at success rates in Phase II studies. Kola, Nature Reviews Drug Discovery 3, 711-715 (2004) states that "more than 70% of oncology compounds" fail their phase II tests, clear evidence preclinical testing does not predict even for passing phase II tests. Figure 1 shows that success rates from first-in-man to registration in oncology is only a 5% rate (based on ten biggest drug companies during 1991–2000). Indeed, given the fact that "biologicals have a higher rate of success from first-in-man to launch — approximately 24%", one would expect that non-biologics in oncology, as is seen here, would have an even lower success rate than that 5%. "The predictive quality of standard animal models has been assessed in a retrospective analysis, with the conclusion that tumor specificity does not translate from laboratory to clinic. Human tumor xenografts that present tumors of a particular histology and tissue of origin do not predict for clinical activity in that tumor." Cancer Drug Design and

Discovery Neidle, Stephen, ed. (Elsevier/Academic Press, 2008) page 427. In other words, successful animal tests with human tumor xenografts with cancer X do not predict clinical success in humans with cancer X.

Indeed, oncologists don't even expect such tests to be reliable predictors. "Cell lines derived under artificial conditions and propagated for decades are not likely to be realistic, or to provide meaningful targets." Cancer Drug Design and Discovery Neidle, Stephen, ed. (Elsevier/Academic Press, 2008) page 428. The obvious limitations of subcutaneously transplanted xenografts are that they do not reside in the same anatomical site as the corresponding tumor in patients (i.e. are not orthotopic); that 'these generally do not metastasize (metastasis is usually how cancers kill patients); that the blood vessels and stroma are of mouse, not human, origin, and that the cells used are from a homogeneous, not heterogeneous, cell type (real world cancers are heterogeneous). Largely as a result, these systems cannot, for example, model drug resistance. "The most common cause of treatment failure of metastatic cancer is drug resistance… Resistance mechanisms remain an undetermined obstacle to the successful discovery and development of novel targeted therapies. The genomic instability that is a hallmark of cancer contributes to the ability of tumors to develop resistance during therapy (acquired resistance), and the intrapatient heterogeneity of most advanced solid tumors invariably leads to the selection of resistant clones (intrinsic resistance)." Cancer Drug Design and Discovery Neidle, Stephen, ed. (Elsevier/Academic Press, 2008) page 430.

It is agreed that considerable success has been achieved in this regard in other areas of medicine, but cancer has been well-recognized as an exception, giving anomalous results. "It should be noted that oncology has the lowest success rates of any therapeutic area." Cancer Drug Design and Discovery Neidle, Stephen, ed. (Elsevier/Academic Press, 2008) page 431. "Clearly, the ability to predict acceptable pharmaceutical properties based on chemical structure would be highly desirable. In an attempt to meet this challenge "Lipinski's Rules" were formulated, based on a retrospective analysis of success rates of new orally administered agents entering early clinical trials .... Interestingly, most commonly used cancer drugs fail to satisfy these criteria....Many marketed anticancer drugs break most of the rules of good pharmacokinetic (PK) behavior." Cancer Drug Design and Discovery Neidle, Stephen, ed. (Elsevier/Academic Press, 2008) page 429.

The examiner is not stating that no individual model provides or will ever provide a good correlation with actual efficacy for any specific cancer type. And it is entirely possible that some present or advanced model e.g. an orthotopic or spontaneous metastasis model can or will be shown to correlate with this or that specific cancer. However, given the art-recognition of the fact that that preclinical models in the cancer area do not correlate with actual treatment, the burden is on applicants to show that their particular model has been shown to correlate with whatever particular cancer they wish to claim. Note here that treatment/inhibition is not claimed for any particular cancer type.

In addition, applicants have not established that their actual numbers constitute what would be considered by one of ordinary skill in the art as a positive result.

In addition, the claims are drawn to what is actually a diverse set of cancers, which have little or nothing in common except that these happen to be at a particular bodily organ or system. By contrast, the testing in the specification is drawn to only a specific cancer or cancers of that organ. Specifically, the effect of celecoxib and curcumin are tested on cell growth of three human colon carcinoma cell lines (HT-29, SW480 and Caco-2) and the c-K-ras-transformed rat intestinal epithelial cell line was assessed alone and in combination. Curcumin and sulindac and curcumin and sulfide and curcumin and nimesulide were similarly tested on the model for colon cancer. It is unclear how these results would translate to successful treatment/inhibition of other cancers, for example, leukemia.

Regarding the rejection over Metaproteomics LLC, Applicants admit that the reference teaches synergistic compositions comprising curcuminoids and NSAIDS such as diterpen lactone species and triterpene species but it does not teach NSAIDs that are recited in the instant claims. As stated supra, . It would have been obvious to substitute the anti-inflammatory agents such as ursolic acid of Metaproteomics LLC for the NSAID sulindac of Samaha et al. Metaproteomics showed that ursolic acid has inflammatory effects and works synergistically with curcumin to treat inflammation and cancer, therefore, it would have been obvious to one of ordinary skill in the art to substitute the sulindac taught in Samaha et al. for the ursolic acid of Metaproteomics

LLC for the predictable result of treatment of colon cancer and inflammation from arthritis (page 1, lines 30-34).

Claim Objections

Claim 13 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 13 recites that the curcumin and NSAID are administered in the same formulation. Claim 12 requires administration of a formulation, thus claim 13 is not further limiting.

Claim Rejections - 35 USC § 112

Claims 1, 3-5, 9-15, 20, 23-25 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating an inflammatory disease or disorder, treating colorectal, prostate, pancreatic and lung cancers, inhibiting cancer cell growth such as the cumin colon carcinoma cell line Caco-2 and HT-29, depicted in the figures and tables, , it does not reasonably provide enablement for treating any "disorder" or any other cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states,

"Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Breath of the Claims and Nature of the Invention: The claims are extremely broad and encompass treating any form of cancer or "disorder". While it appears that Applicant is intending to claim treating an inflammatory disease/disorder, as drafted the claim reasonably is interpreted as treating any disorder (note in the claim the absence of 'or' and the presence of a comma between 'disease' and 'disorder').

Additionally, the invention is extremely complex in that it encompasses the treatment of any cancer or disorder using the claimed compounds. As explained supra, there are many causes for cancer making the treatment this disease unpredictable. Further, the instant specification defines "treatment of cancer" as "prevention for

prophylactic situations for those patients susceptible to contracting cancer" (page 15, lines 9-18).

State of the Prior Art and Level of Skill in the Art: With regards to treating any disorder or treating/preventing caner, the level of skill in the art is low. and the state of the art with regard to prevention and treatment of cancer from any origin with the same agent(s) is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein cancer was predictably prevented because cancer is a diverse class of diseases which differ widely in their causes and biology, nor are there any examples of treating any and all cancers with a single compound due to the diversity of the cancers. Current evidence indicates that cancers are caused by abnormalities in the genetic material of the transformed cells. These abnormalities may be due to the effects of carcinogens, such as tobacco smoke, radiation, chemicals, or infectious agents. Other cancer-promoting genetic abnormalities may randomly occur through errors in DNA replication, or are inherited, and thus present in all cells from birth. The heritability of cancers is usually affected by complex interactions between carcinogens and the host's genome. Also, cancer affects people at all ages with the risk for most types increasing with age. Each of these defects may or may not be addressed by the administration of the claimed compounds.

Predictability of the Art, Guidance of the Specification and Working Examples: The lack of significant guidance from the specification or prior art with regard to the actual prevention of cancer or reducing the likelihood of contracting cancer

in a subject susceptible to contracting said disease makes practicing the claimed invention unpredictable in terms of prevention or treatment or prophylaxis of cancer, even in a subject that is susceptible to the disease. The guidance given by the specification as to how one would administer the claimed compounds to a subject in order to actually prevent cancer is minimal. All of the guidance is drawn to prophylactic situations wherein it is unclear whether one would have contracted cancer without the administration of the composition of curcumin and a NSAID. All of the working examples provided by the specification are drawn to in vitro effects on cancer cell lines. Additionally, the specification fails to provide a nexus between the model cell lines for colorectal, prostate, lung and pancreatic cancers and all other cancers and disorders. The art is additionally absent of any teaching that such cell lines are the are recognized model system for any and all cancers and disorders.

H. The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for prevention or treatment of cancer, reducing the likelihood of contracting cancer and treating any 'disorder'. If unsuccessful, which is likely, given the lack of significant guidance from the specification or prior art with regard to the predictable prevention of cancer with any compound, one of skill in the art would have to then either envision a modification of the curcumin and NSAID, dosage,

duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance from the specification of prior art regarding prevention of cancer, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to prevent the development of cancer or reduce the likelihood of developing cancer in a susceptible subject or treating any 'disorder' by administration of a combination of the NSAID and curcumin.

Therefore, a method of treating, inhibiting and reducing the likelihood of contracting of cancer, other than colorectal, prostate, pancreatic and lung cancers, and treating any 'disorder' in an individual by administering an NSAID and curcumin is not considered to be enabled by the instant specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 9-11 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites the limitation "wherein said curcumin is a curcumin analogue or derivative" in lines 1-2 of the claim. There is insufficient antecedent basis for this

limitation in the claim because it depends from instant claim 1 drawn to the compound "curcumin" and not to an analogue or derivative. Claim 5 is impermissibly broader than claim 1 by claiming curcumin analogues or derivatives.

Claims 9-11 recite the limitation "the method according to claim 6" in line one of each of the claims. There is insufficient antecedent basis for this limitation in the claim because instant claim 6 has been cancelled.

Claims 14 and 15 recite that the cells are contacted with a formulation comprising curcumin followed by contacting with a second formulation containing the NSAID (or the reverse, in claim 15). There is insufficient antecedent basis for this in the independent claim, as claim 12 is drawn to administering a formulation, not multiple formulations.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 12 is rejected under 35 U.S.C. 102(b) as being anticipated by Thun et al. (JNCI, 2002).

Thun et al. teach the combination of sulindac and curcumin for inhibiting colon cancer (see page 260, table 2).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 4, 10, 12-15, 20, 21, 25 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thun et al. (JNCI, 2002) and Kawamori et al. (Cancer Research Vol. 59, 597–601, February 1, 1999).

Thun et al. teach administration of anti-inflammatory drugs such as sulindac and celecoxib to inhibit the growth of adenomatous polyps and to some extent, other cancers (see abstract). Thun et al. further teaches that a strategy to improve the balance of benefits and risks associated with NSAID use is to identify combinations of drugs that are effective at very low doses (page 255, column 2, first full paragraph) (addressing instant claim 1, drawn to reducing the NSAID concentration needed while maintaining the same therapeutic effects as compared to administering the NSAID alone) and further exemplifies the combination of either sulindac, aspirin or piroxicam (addressing instant claim 11, drawn to a NSAID other than sulindac, celecoxib, sulindac sulfide or derivatives, analogues, salts or prodrugs thereof) with curcumin (page 255, column 2, first full paragraph).

Kawamori et al. teach that curcumin inhibits chemically induced carcinogenesis in the skin, forestomach, and colon when administered prior to, during and after carcinogen treatment as well as during the promotion/progression phase of colon carcinogenesis (see abstract). Curcumin was shown to inhibit colon carcinogenesis through the modulation of COX activity in the tumor tissue (page 597, column 2 last paragraph) and it is suggested that curcumin acts on pathways that may inhibit cell proliferation and enhance apoptosis (treatment of cancer) (page 598, column 1).

Kawamori et al. teach that Curcumin has a strong inhibitory effect on cell proliferation in the HT-29 and HCT-15 human colon cancer cell lines (page 597, column 2) and further teach that several inhibitors of PG synthesis, such as aspirin, ibuprofen, sulindac and piroxicam suppress colon carcinogenesis in laboratory animal model assays and inhibition of colon carcinogenesis was consistently associated with a decrease in the activity of COX in colon tumors (page 597 column 2 to 598, column 1). Thun et al. teach the effectiveness of NSAIDS, such as celecoxib and sulindac for treatment of colon cancer and suggest the combination of curcumin. Kawamori et al. teach the effectiveness of curcumin in treatment and inhibition of colon cancer and teach that NSAIDs are also effective.

As stated in In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980): It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960). As this court explained in *Crockett*, the idea of combining them flows logically from their having been individually taught in the prior art.

Addressing instant claim 9 wherein curcumin and NSAID are not administered within the same formulation, claim 13, wherein cells are contacted with a single formulation comprising both curcumin and at least one NSAID, claim 14 drawn to administering curcumin followed by the NSAID and claim 15, drawn to administering a

NSAID followed by curcumin, "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation (see MPEP § 2144.05). In the absence of any criticality and/or unexpected results from the manner of administering the agents, the instant invention is considered obvious.

Regarding the limitation of instant claims 14 and 15, drawn to the administration of the curcumin followed by the NSAID or the NSAID followed by the curcumin, there is no asserted criticality in the order of administration and as such, the order of administration is considered to be intrinsic motivated by the teaching of Thun et al. who teaches administration of sulindac and curcumin for treatment of patients with an average or above average risk of colon cancer.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the foregoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1, 3-5, 9-15, 20, 21, 23-25 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Metaproteomics LLC WO 03/007975 A1 and Samaha et al. (Cancer Research, 1997).

Metaproteomics teach synergistic compositions comprising curcuminoids and non steroidal anti-inflammatory agents (NSAIDs) such as diterpene lactone species and triterpene species, known for their anti-inflammatory properties, (page 3, lines 18-25) for the treatment of inflammatory diseases such as arthritis (page 1, lines 30-34) and treatment of cancer such as colorectal cancer (page 2, lines 1-3). It further teaches the desire to discover compounds can be administered together such that they are synergistic so that they can be used at sufficiently low doses with no adverse side effects and wherein the COX-2 specificity is < 5-fold (page 3, lines 26-33,). Demethoxycurcumin and bisdemethoxycurcumin are disclosed as curcumins that are included in the invention (page 8, lines 15-17) (claim 5). Regarding claims drawn to administration of the agents separately or together, Tables 8 and 9 teaches administration of first compound (curcumin), second compound (oleanolic acid) and the two components combined (tables 8 and 9, page 22). Addressing instant claim 11, drawn to the NSAID selected from one that is "other than sulindac, celecoxib or sulindac sulfide, Metaproteomics LLC teach the combination of curcumin with a diterpene lactone or triterpene NSAID, such as ursolic acid. Addressing instant claim 14 drawn to contacting cells with a formulation containing curcumin and at least one NSAID, Example 8 (page 25) teaches treatment of colon cancer comprising administration of the composition. Addressing instant claims 22 and 33, drawn to the pharmaceutical

composition comprising curcumin and at least one NSAID and a pharmaceutically acceptable carrier, excipient or diluent, Metaproteomics LLC teach the compositions formulated in a pharmaceutically acceptable carrier (page 26, lines 25-29). It further teaches the desire to formulate compounds can be administered together such that they are synergistic so that they can be used as sufficiently low doses with no adverse side effects and wherein the COX-2 specificity is < 5-fold (page 3, lines 26-33).

While Metaproteomics teaches administration of curcumin and a COX2 inhibitor to treat colon cancer or inflammation, it does not teach the NSAIDS selected from, for example sulindac. However, Samaha et al. teach that sulindac is a NSAID (page 1301, columns 1 bridging to column 2). It is prima facie obvious to substitute equivalents, motivated by the reasonable expectation that the respective species will behave in a comparable manner or give comparable results in comparable circumstances. Since Metaproteomics teaches that the COX-2 inhibitors were effective especially when combined with curcuminoids (see page 11, lines 1-9) there is a reasonable expectation that other NSAID COX-2 inhibitors would be effective also. The express suggestion to substitute one NSAID for another need not be present to render the substitution obvious. It would have been obvious to substitute the anti-inflammatory agents such as ursolic acid of Metaproteomics LLC for the NSAID sulindac of Samaha et al. Metaproteomics showed that ursolic acid has inflammatory effects and works synergistically with curcumin to treat inflammation and cancer, therefore, it would have been obvious to one of ordinary skill in the art to substitute the sulindac taught in

Samaha et al. for the ursolic acid of Metaproteomics LLC for the predictable result of treatment of colon cancer and inflammation from arthritis (page 1, lines 30-34).

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the foregoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne (Bonnie) Eyler can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Donna Jagoe /D. J./
Examiner
Art Unit 1619

September 6, 2010

/Andrew D Kosar/
Primary Examiner, Art Unit 1654